

Claim Rejections and resultant modifications in claim 7 above

Claim 3:

EXAMINER- "It is unclear from the claim language as to what structural elements are being used to determine that a 50-90% or more washout of nitrogen from the body and body water and a subsequent washout of nitrogen from the affected tissues and mitochondria permits the return of ischemic tissues to a state of oxidative metabolism," has occurred.

RESPONSE: Applicant based his determinations of nitrogen washout on a literature value of 18ml per minute and a calculated total body water nitrogen content of 1050ml for an above average 220 pound stroke patient. Therefore, 1050 ml/18 ml per minute calculates to about 58 minutes. Allowing for some exponential tail near the end, applicant allows 60-90 minutes or slightly longer for complete body washout. See instant application paragraph [0007]. Evidence that washout has been successfully extended to the stroke affected tissues and mitochondria and has permitted the return of oxidative metabolism to the tissues would be based on clinical recovery from stroke, i.e. if oxidative metabolism is not returned to the ischemic tissues they will die and areas of brain death can be delineated by MRI imaging technology. Recently completed animal studies have verified the utility of the instant invention and are included in applicant's new information disclosure statement. It was shown that control animals breathing 30% oxygen and 70% nitrogen suffered a 36% stroke of the ipsilateral brain hemisphere compared to only 4% in those that breathed 30% oxygen and 70% helium, an 87% improvement in recovery. Since the test group shows a dramatic improvement in

recovery, it is clear, by scientific process of elimination, that oxidative metabolism had to return to said tissues for the recovery to ensue. Note: These expanded changes taken from the specification [0007] are now reflected in new claim 7.

Claim 4:

EXAMINER: It is unclear as to what time frame would be sufficient and what applicant intends when stating that the “treatment is implemented as soon as possible.”

RESPONSE: There is wide variability between hospitals and among departments and individual physicians in the handling of individual patients, i.e. an inherent part of medical practice. Generally, following admission, stroke patients are stabilized as to cardiovascular and respiratory parameters and then scored for various stroke indices e.g. NIH Stroke Scale, Glasgow Coma Scale, Hunt and Hess Scale, Modified Rankin Scale, and the Barthel Index. To the extent that some or all of these indices are utilized in early evaluation of patients, there will be a delay in diagnostic imaging. At the earliest time possible imaging is carried out using computed tomography (CT) to rule out hemorrhage and indicate an ischemic stroke. Only at this point does it become medically rational to institute the nitrogen washout procedure of the instant invention. There is great effort being directed at early CT in order to allow the administration of thrombolytic drugs, which are contraindicated in hemorrhagic stroke. (See Marler, Information Disclosure Statement of 11/03/06)

Although this is the earliest point at which one should initiate the nitrogen washout, perhaps 30-60 minutes after admission, there may be other extenuating circumstances which could further delay initiation of the washout in selected patients. Hence, the

wording “as soon as possible following admission” in claim 8.

It is not the prerogative of the inventor to dictate medical practice and it is to be expected that each institution will employ the procedure in a way that optimizes their own experience. Moreover, realizing that the return of blood flow must be within the first few (about 6-8) hours for significant recovery from stroke prior to the onset of brain tissue death, the continuation of the therapy for up to 72 hours is stipulated to allow recovering brain tissue to stabilize prior to the re-introduction of nitrogen into the inhaled air. See instant application, paragraph [0008].

Applicant believes that canceling of claims 3-6 and replacing them with new claims 7 through 10, coupled with the above commentary, has traversed examiner’s objections under 35 USC, paragraph 112.

REBUTTAL TO FINAL REJECTION NOTICE:

Applicant respectfully traverses the rejection as applied to the newly added claims 7-10 as being obvious over Kumar et al (20003013844) in view of Bird et al (3688794).

Reconsideration is respectfully requested.

Note: Herein all references to the instant application published as 20040142044 will refer to paragraphs in brackets. References to Kumar et al published as 20030131844 will be by numbers only.

EXAMINER quotes main items from Kumar as paragraphs 0121, 0032, 0014 and 0114.

Kumar- 0121 “Injury can be minimized and recovery hastened when hypothermia is instituted early following heart attacks and strokes.”

RESPONSE: This single sentence has several deficiencies which negate its relevance to the instant application as specified in new claim 7 above.

A. “Injury” is a non-specific term which is indeterminate compared to applicant claim 7 wording- “causing an impairment in oxidative metabolism in said mitochondria and stroke-affected tissues”, and for the record, the word mitochondria does not appear anywhere in Kumar et al. Therefore, the target of the instant invention, mitochondria, is not considered of enough relevance to be mentioned in the 34 claims or 131 paragraphs of the Kumar et al application. Therefore, Kumar is non-specific with respect to how injury is to be minimized.

B. “recovery hastened” again non-specific, what are the Kumar criteria for recovery?

The instant application claim 7 indicates recovery to be “until and beyond the time that blood flow is restored to the stroke-affected compromised tissues, to permit a secondary reverse-gradient washout of nitrogen from said tissues and said hypoxic mitochondria thereby allowing the mitochondria and said tissues to re-access oxygen and return to a state of oxidative metabolism.”

C. “hypothermia” the effective methodology of Kumar is not mentioned anywhere in the instant application; the mechanisms are indeed different. Hypothermia lowers the metabolism of the entire body including the stroke-affected tissues. The instant application Claim 7 “allowing the mitochondria of said tissues to re-access oxygen and return to a state of oxidative metabolism.” has as its goal an increase in the metabolism of the stroke-affected tissues, not a decrease as in Kumar, 0002- “for purposes including decreasing tissue oxygen consumption.”

D. Kumar “following heart attacks and strokes.” Kumar does not differentiate strokes and therein indicates efficacy for all strokes. The instant invention claim 7 indicates value for treatment of reversible ischemic cerebrovascular accident (stroke) and thereby excludes hemorrhagic strokes which are not reversible.

Kumar- 0032 This paragraph mentions using a face mask tube for administration of cooled gases.

Response See paragraph [0010] of the instant application. “The hardware, gas cylinders, gas mixing technology, one-way flutter valves and other ancillary equipment required to practice this invention are known in the art and are not part of this invention.”

The invention is the reversing of the heretofore unknown trapping of nitrogen by hypoxic

mitochondria in stroke-affected tissues in order to allow oxygen to regain access to the interior of said mitochondria and thereby reestablish oxidative metabolism in said tissues.

Kumar -0014 “In order to avoid hypoxemia, the concentration of oxygen in the inspired gas mixture is preferably kept to at least 20%, with the remainder of the gas mixture preferably being helium. The heat loss from the lungs is intensified by addition of perfluorocarbon mist or liquid to the inspired gases. The phase change of the perfluorocarbon from liquid from gas extracts a significant amount of heat from the lungs due to the latent heat of vaporization.”

Response This paragraph deals with lowering the temperature of the inspired gases. As such, it reads outside the specification and claims of the instant invention. Generally, composition of matter claims are regarded as the strongest and most important claims in a patent application. In Kumar et al, Claims 28-34 are composition claims. Claim 30 reads “A composition of matter as in claim 29, wherein the oxygen gas is present in a concentration of at least 17 volume percent. Thereby, Kumar et al claims as the only composition of matter involving oxygen concentrations, a concentration of at least 17 volumes percent. This reads against paragraph 0014 wording- “is preferably kept to at least 20%,”. Clearly, the claim is outside of the paragraph 0014 specification, placing the wording of paragraph 14 somewhat in doubt, and certainly removes the composition of matter claim of Kumar et al from impacting applicant’s Claim 7.

Kumar 0114 The expired gas can be respired through an expiratory one-way valve.

Response: See response above to paragraph 0032 of Kumar.

General Disparities and paragraphs of Kumar which teach away from the instant invention.

All 34 claims in the Kumar application and all paragraphs in the specification which address helium/oxygen gas mixtures detail descriptions of cooled gases or in some cases warmed gases. Cooling or heating of gases is not indicated in the instant application, and therefore the use of such gases in treating stroke in a manner analogous to that of the instant application is not anticipated by Kumar. Whereas hypothermia decreases metabolism, the instant invention returns (increases) the affected tissues to normal metabolic activity. The mechanism of action of Kumar et al gas mixtures 0002 is to decrease tissue oxygen consumption by employing the inspiration of cooled gases and perfluorocarbons. This is counter to the instant invention which proposes to increase the oxygen utilization of the stroke affected tissues by clearing nitrogen from the mitochondria in said tissues.

It is a well known principal of Chemistry that gases become more soluble in water as its temperature is lowered. Therefore, as Kumar et al lower the temperature of the body using cooled gases, the body water will cool which increases the solubility and lowers the vapor pressure of the dissolved gases. In turn this will slow the exchange of tissue gases with the circulating blood and slow the nitrogen washout kinetics to an extent that the instant invention could be made ineffective in the approximate 1-3 hour window of opportunity (see [0007] and claim 7).

Perhaps most important re Kumar are embodiments 0031, 0053, 0085, 0098, 0100, 0103, which, if employed, would totally negate the utility of the instant invention.

All six of these paragraphs deal with adding nitrogen to the inhaled gas mixture, or re-breathing systems which allow the return of exhaled nitrogen back to the lungs.

These embodiments of Kumar would preclude the washout of nitrogen and are forbidden by applicant's instant specification: paragraphs [0005] "The scenario then becomes a simple matter of eliminating nitrogen from the inhaled gas mixtures and replacing it with a gas or gases which will facilitate nitrogen washout", and [0006] "Any gas formulation which has as its main purpose the washout of nitrogen from the body would surely be devoid of nitrogen per se. And "The specific concentrations of the two gases within the ranges specified above would not be as important as the exclusion of nitrogen from the mixture and the specific nitrogen washout technique described below." And "exhaled gases would be shunted to ambient atmosphere through a one-way flutter valve."

The above paragraphs of Kumar 0031, 0053, 0085, 0098, 0100, 0103 allow nitrogen breathing or re-breathing, which would defeat the nitrogen washout strategy of the instant invention. Applicant therefore contends that these paragraphs, taken alone, teach away from the instant invention to an extent to make it inoperative. Hence, Kumar et al must be rejected as relevant prior art against to the instant invention.

Kumar et al, duration of treatment:

Claim 6 -sustain life for at least a one hour procedure, 0019 suggests 20 minutes, 0094 short term hypothermia, lasting several hours to a few days, 0120 several hours, 0121 prolonged use in space travel.

Clearly, Kumar et al is all over the map with suggested times for use of hypothermia and

with no guidelines or criteria as to when to terminate the process. Moreover, Kumar et al have no mention as to specific time frames on when to initiate and/or terminate hypothermia as a treatment for stroke.

Applicant clearly states in claim 8, that treatment is implemented as soon as possible following admission to the hospital, which dictates subsequent to imaging to rule hemorrhagic stroke, and that it is continued for up to 72 hours to assure optimum therapy and minimize cell death. See applicant specification paragraph [0008].

“The extended time frame beyond 1-2 hours for inhaling the gas mixture and continuing nitrogen washout may be a clinical decision to assure that mitochondrial metabolism and mitochondrial membrane repair, function and stability have been fully restored to levels wherein the re-introduction of high concentrations of inhaled nitrogen would not re-aggravate the ischemic injury.” The exact determination of the most appropriate time frames will await years of clinical and medical use experience.

NONOBVIOUSNESS:

1504.03 Nonobviousness [R-2] – 1500 Design Patents

B. Ascertaining the differences between the claimed invention and the prior art..

The above discussion outlines numerous differences and inconsistencies between the instant application and Kumar et al. which applicant contends (Il. Prima Facie Obviousness) do not stand the tests. “As a whole, a design must be compared with something in existence, and not something brought into existence by selecting and combining features from prior art references” Applicant contends that lack of consideration of Kumar, paragraphs 31,53,85,98,100 and 103, which would make the

instant invention unworkable constitutes “selecting” of some embodiments while ignoring a large number of embodiments which simply won’t work.

In the Yardley decision, it was stated that – “ Therefore, in order to support a holding of obviousness, a basic reference must be more than a design concept; it must have an appearance substantially the same as the claimed design”. “Absent such a reference, no holding of obviousness can be made, whether based on a single reference alone or in view of modifications suggested by secondary prior art.”

Examination of the details of Kumar versus the instant application reveals little, if anything, of identical use parameters, and details a number of embodiments in Kumar which would teach away and nullify the utility of the instant application. To establish prima facie obviousness, all the claim limitations must be taught or suggested by the prior art.

Claim 7 limits the use of the instant nitrogen washout procedure to patients who have suffered an ischemic stroke; Kumar claims all strokes.

Claim 7 denotes value for the process to correct the heretofore unknown trapping of nitrogen in hypoxic mitochondria. Kumar (filed July 17, 2003) could not have been aware of this scientific information until applicant’s application was published on (July 22, 2004) or applicant’s publication in Medical Hypothesis in early (Feb) 2004.

A copy of this article is provided in the information disclosure by applicant.

Claim 7 indicates that the nitrogen washout from the hypoxic mitochondria occurs following a restoration of blood flow to the ischemic brain tissue, Kumar et al do not address the return of blood flow in their application.

Claim 7 indicates the goal of returning oxidative metabolism to hypoxic mitochondria.

Kumar does not use the word mitochondria. Moreover, Kumar et al have as their primary goal a reduction of metabolism in the entire body, including mitochondria, i.e. counter to claim 7.

Claim 8 indicates that the procedure be implemented as soon as possible after admission to the hospital, and as explained above that mandates at a minimum that imaging (CT scanning) be completed in order to insure that the stroke is ischemic, not hemorrhagic.

Kumar et al make no such differentiation. Nor does Kumar have any specific time frames for onset or duration of stroke or any other treatment, opting instead to list a number of sites where treatment can be implemented.

Resolving the level of ordinary skill in the art:

-the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains.

Under Nonobviousness 15.68 it is stated...“Further, it is noted that a designer skilled in the art is charged with knowledge of the related art; therefore, the combination of old elements, herein, would have been well within the level of ordinary skill.” Thus, it is implied that Kumar et al, published in 2003, when coupled to Bird et al, would have taught all of the embodiments of the instant application to neurologist practitioners (charged with knowledge of the related art in treating stroke), that one could safely and effectively treat stroke by using the readily available and simple technique of total body washout of nitrogen. We are now approaching mid-2007 and no reports of stroke patients being availed of this “obvious” breakthrough have surfaced since applicant’s 2004 publication. Does this mean that all neurologists are guilty of malpractice? Of course not,

medicine doesn't work that way. Even though heliox has a long history of safe use, its efficacy for treating stroke awaited a reduction to practice study. Applicant made perhaps a dozen or more contacts in 2004 and 2005 to interest potential collaborators in industry, academia and government with the consistent response- come back when you have some animal data. In the fall of 2005 a contact was made at St. Louis University and a collaboration on a stroke model study in rats was begun. Toward the end of 2006 the study was completed and the results will be presented in May 2007 at the American Academy of Neurology meetings in Boston. This study shows an 87% reduction in the severity of stroke in a heliox (30% oxygen/70% helium) group of animals versus a control group breathing 30% oxygen and 70% nitrogen (see new information disclosure statement). When this presentation occurs, only then will it become obvious to those skilled in the art that the process has merit and one can then expect that a number of grant applications to support human clinical trials will follow.

What applicant claims is; absent the new knowledge of the instant invention and information disclosures that there exists a medical need for washout of nitrogen from hypoxic mitochondria in ischemic stroke, no one would practice the invention regardless of any close, but not enabling, prior art. The discovery of nitrogen accumulation in hypoxic mitochondria by inventor enables the washout treatment by providing the scientific rationale for the procedure.

For all of the above reasons applicant submits that new claims 7-10 are not disclosed by the cited references and respectfully requests allowance of all of the claims.